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EXAMINER	
GUDIBANDE, SATYANARAYAN R	

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

## Office Action Summary

Application No.

10/522,222

Applicant(s)

FERGUSON ET AL.

Examiner

Satyanarayana R. Gudibande

Art Unit

1654

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 16 April 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-17 is/are pending in the application.
- 4a) Of the above claim(s) 6,7,9-11 and 15-17 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-5,8 and 12-14 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |   |   |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)  | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date <u>4/28/05, 6/23/05</u> | 6) <input type="checkbox"/> Other: _____  |

### **DETAILED ACTION**

Applicants amend claim 8 to depend from claim 1 instead of claim 15 as originally filed. Applicants request that claims 8-11 be examined on the merit as they belong to group I invention now after the amendment.

#### ***Election/Restrictions***

Applicant's election without traverse of group I invention (claims 1-7 and 12-14) in the reply filed on 4/16/07 is acknowledged.

Applicants have drawn attention to an amendment to correct a typographical error in the previous set of claim and thereby request the examination of claims 8-11. Applicant's request has been granted and claims 8-11 will be included in the examination. However, applicants request to examine the genus of furin inhibitors would be burdensome for the office as it involve unreasonable burdensome search of structurally distinct compounds (applicants have admitted that the genus of furin inhibitors disclosed in the specification are chemically distinct compounds, see page 4, paragraph 5 of remarks filed on 4/16/07).

Applicant's election with traverse of the species pulmonary fibrosis in the genus of fibrotic disorder in the reply filed on 4/16/07 is acknowledged. The traversal is on the ground(s) that the examination of the genus of fibrotic disorder would not be an unreasonable burden. However, applicants acknowledge that the fibrotic disorders such as pulmonary fibrosis, glomerulonephritis, cirrhosis of the liver, fibrocytic disease conditions disclosed in the specification differ in patient population and etiology of the disease. Therefore, searching for one

Art Unit: 1654

disorder associated with one fibrotic disorder would not automatically yield information about the other disorders and other method for treatment and additionally it involves different patient population.

The inventions restricted are patentably distinct. The search for each of the inventions is not co-extensive particularly with regard to the literature search. Burden consists not only of specific searching of classes and subclasses, but also of searching multiple databases for foreign references and literature searches. Burden also resides in the examination of independent claim sets for clarity, enablement, and double patenting issues. Further, a reference that would anticipate the invention of one group would not necessarily anticipate or even make obvious another group. Finally, the consideration for patentability is different in each case. Thus, it would be an undue burden to examine all of the above inventions in one application and the restriction for examination purposes as indicated above is deemed proper. A search for the combination of all the furin inhibitors that are chemically distinct molecules and all the fibrotic disorders would place unreasonable burden on the office. The restriction requirement is still deemed proper and is therefore made FINAL.

Claims 1-17 are pending.

Claims 6, 7 and 9-11 have been withdrawn from further consideration as being drawn to non-elected species.

Claims 15-17 have been withdrawn from further consideration as being drawn to non-elected invention.

Claims 1-5, 8 and 12-14 are examined on the merit.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 8 and 12-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Canadian Patent Application CA 2312109 of Dubois.

In the instant application, applicants claim a method for reducing scarring during the healing of wounds, reducing fibrosis in the treatment of fibrotic conditions, or for preventing or inhibiting scar formation or fibrosis, comprising applying a furin inhibitor to a site of a wound or fibrotic disorder or to a site where a wound may form or fibrosis may occur.

Dubois discloses a protein-based protease inhibitor that is a mutant of serpin  $\alpha 1$ -antitrypsin wherein the reactive site has Arg-Ile-Pro-Arg<sup>358</sup> sequence (known as PDX). This mutant has been shown to be a potent furin inhibitor (page 5, paragraph 2). The reference also discloses PDX or a construct, variant, analog, peptide, peptidomimetic, salt and derivatives thereof in the preparation of pharmaceutical compositions for the inhibition of furin or furin-like protease activity in inflammatory and erosive diseases that includes pulmonary fibrosis, abnormal wound healing and arthritis and others (Page 8, paragraph 2). Furin or furin-like protease activity includes the activity of proprotein convertases such as PACE4, PC $\alpha$ 6 or PC7 (page 8, paragraphs 1 and 2). This meets the limitations of claims 1, 2, 8 and 12-14. The reference also discloses pharmaceutical composition of that includes compositions with viscous paraffin, fatty acid mono and diglycerides (page 13, paragraph 1) and use of non-aqueous

Art Unit: 1654

vehicles such as cottonseed oil and other oils (page 14, paragraph 1) that are useful in solubilizing lipid soluble active agents. This meets the limitations of claim 3. The cited reference teaches the use of PDX or a construct, variant, analog, peptide, peptidomimetic, salt complex derivative thereof for abnormal wound healing with furin or furin-like inhibitors, therefore, it inherently reduces scarring during healing of wounds (page 8, paragraphs 1 and 2). Therefore, the claims 1-3, 8 and 12-14 of instant application are anticipated by the cited reference of Dubois.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Art Unit: 1654

Claims 4, 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dubois as applied to claims 1-3, 8 and 12-14 above, and further in view of Pearton, et al., 2001, Exp Dermatology, 10, 193-203.

In the instant application, applicants claim a method for reducing scarring during the healing of wounds, reducing fibrosis in the treatment of fibrotic conditions, or for preventing or inhibiting scar formation or fibrosis, comprising applying a furin inhibitor to a site of a wound or fibrotic disorder or to a site where a wound may form or fibrosis may occur.

Dubois discloses a protein-based protease inhibitor that is a mutant of serpin  $\alpha 1$ -antitrypsin wherein the reactive site has Arg-Ile-Pro-Arg<sup>358</sup> sequence (also known as PDX). This mutant has been shown to be a potent furin inhibitor (page 5, paragraph 2). The reference also discloses PDX or a construct, variant, analog, peptide, peptidomimetic, salt and derivatives thereof in the preparation of pharmaceutical compositions for the inhibition of furin or furin-like protease activity in inflammatory and erosive diseases that includes pulmonary fibrosis, abnormal wound healing and arthritis and others. Furin or furin-like protease activity includes the activity of proprotein convertases such as PACE4, PC5/6 or PC7/8 (page 8, paragraphs 1 and 2). This meets the limitations of claims 1, 2, 8 and 12-14. The reference also discloses pharmaceutical composition of that includes compositions with viscous paraffin, fatty acid mono and diglycerides (page 13, paragraph 1) and use of non-aqueous vehicles such as cottonseed oil and other oils (page 14, paragraph 1) that are useful in solubilizing lipid soluble active agents. This meets the limitations of claim 3. Although, the reference of Dubois discloses PDX or a construct, variant, analog, peptide, peptidomimetic, salt and derivatives thereof in the preparation

Art Unit: 1654

of pharmaceutical compositions for the inhibition of furin or furin-like protease activity, it does not specifically disclose the elected species decanoyl-RVKR-cmk.

Pearton, et al., discloses the elected species decanoyl-RVKR-cmk. The cited reference of Pearton teaches that the decanoyl-RVKR-cmk as a peptide PC inhibitor inhibits the cleavage of Notch-1, a receptor important in cell fate determination and is found throughout the epidermis (Abstract). The decanoyl-RVKR-cmk is a chloromethyl ketone peptide. The reference teaches that a protease family that has been implicated in processing and differentiation in a number of tissues is the Proprotein Convertase (PC) family. Furin (also known as PACE), PACE4, PC5/6 or PC7/8 belongs to this proprotein Convertase (PC) family. The PC enzymes recognize basic motifs, cleaving after paired basic residues (PC2 and PC1/3) or after a canonical RX(R/K)R motif (furin and PACE4). Furin has been shown to process a wide variety of substrates including receptors, growth factors, hormones, plasma proteins, matrix metalloproteinases and extracellular matrix components. Several proteins relevant to keratinocyte development have been shown to be substrates for PC processing or contain potential PC cleavage sites that include receptors such as Notch-1 receptors (page 193 column 2, and 194 column 1). Pearton, et al., tested the inhibition of furin with decanoyl-RVKR-cmk in the processing of Notch-1 receptor that has a key role in the cell fate determination and patterning. The inhibition of the processing of Notch-1 from the precursor form (220kDa) to the functional 120 kDa was observed indicating the inhibition of the furin, which is a proprotein Convertase (page 199, column 2, paragraph 2). The fact that decanoyl-RVKR-cmk is a peptide chloromethyl ketone and inhibits furin, which is a proprotein Convertase meets, the limitations of claims 4 and 5. The reference of Pearton teaches



Art Unit: 1654

that the Decanoyl-RVKR-CMK is a **cell permeable** PC inhibitor (page 199, column 2, paragraph 2).

It would have been obvious to one of ordinary skill in the art to modify the methods taught by Dubois and Pearton, et al., in order to develop a method for reducing scarring during the healing of wounds, reducing fibrosis in the treatment of fibrotic conditions, or for preventing or inhibiting scar formation or fibrosis, comprising applying a furin inhibitor to a site of a wound or fibrotic disorder. Because, Dubois teaches the composition of protein based protease inhibitors for furin and furin-like activity and Pearton teaches that decanoyl-RVKR-cmk inhibits the activity of furin a PC enzyme. The motivation comes from the fact that Dubois teaches use of PDX or a construct, **variant, analog, peptide, peptidomimetic, salt and derivatives thereof** in the preparation of pharmaceutical compositions for the inhibition of furin or furin-like protease activity in inflammatory and erosive diseases that includes pulmonary fibrosis, abnormal wound healing and arthritis and others and Pearton teaches that decanoyl-RVKR-cmk is a peptide chromomethyl ketone and inhibits furin which is a proprotein Convertase that inhibits the processing of Notch-1 receptor that is involved in the cell fate determination and patterning of epidermis. Also, that the Decanoyl-RVKR-CMK is a **cell permeable** PC inhibitor. Cited reference of Pearton also teaches that proprotein convertases (PCs) may play multiple roles during the differentiation of cells within the epidermis (page 202, column 1, paragraph 2). There would have been reasonable expectation of success given the fact that Dubois taught that analogs, peptides and peptide mimetics of PDX could be used in formulations for the inhibition of furin or furin-like protease activity and the fact that the elected species of the instant invention was used in the inhibition of furin to inhibit the processing of Notch-1 receptor that is key in the

Art Unit: 1654

cell fate determination and patterning of epidermis. The fact the Decanoyl-RVKR-CMK is a **cell permeable** PC inhibitor, one would have reasonable expectation to use this analog of the furin inhibitor as it has been shown to be a good cell permeation property compared to other analogs, variants, salts or derivatives thereof.

Therefore, the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 8 and 12-14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Because, in the instant application claim a method for reducing scarring during the healing of wounds, reducing fibrosis in the treatment of fibrotic conditions, or for preventing or inhibiting scar formation or fibrosis, comprising applying a furin inhibitor to a site of a wound or fibrotic disorder or to a site where a wound may form or fibrosis may occur. The claims as recited include any and all furin inhibitors for reducing variety of scars during healing of wounds, reducing fibrosis in the treatment of any and all fibrotic conditions or

Art Unit: 1654

disorders and also in preventing or inhibiting formation of fibrosis or scars including at sites where a wound or fibrosis may form or occur.

The MPEP clearly states that the purpose of the written description is to ensure that the inventor had possession of invention as of the filing date of the application, of the subject matter later claimed by him. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir.1997). The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the application. These include, "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed invention is sufficient" MPEP 2163.

In the instant application, applicants claim a method for reducing scarring during the healing of wounds, reducing fibrosis in the treatment of fibrotic conditions, or for preventing or inhibiting scar formation or fibrosis, comprising applying a furin inhibitor to a site of a wound or fibrotic disorder or to a site where a wound may form or fibrosis may occur.

The claims as recited and as previously stated include any and all furin inhibitors. The specification lists several classes of compounds as Convertase inhibitors (page 9 of the

Art Unit: 1654

specification) that in turn contain many species of inhibitors. The classes of compounds and species within the disclosed classes belong to different classes of biomolecules such as DNA, proteins, peptides, hormones, ribozymes, antisense DNA and organic molecules. Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In Regents of the University of California v. Eli Lilly & Co., the court stated: “A written description of an invention involving a chemical genus, like a description of a chemical species, ‘requires a precise definition, such as by structure, formula, [or] chemical name,’ of the claimed subject matter sufficient to distinguish it from other materials. However, in the instant case, the specification does not provide any examples or structural characteristics associated with these classes or species of inhibitors. The specification only provides the structural features of two inhibitors and they are decanoly-RVKR-cmk and hexa-arginine. The class of compounds and species within the disclosed classes belong to different classes of biomolecules such as DNA, proteins, peptides, hormones, ribozymes, antisense DNA and organic molecules. Therefore, the “furin inhibitors” as claimed in the present invention represent innumerable chemical compounds and molecules with widely varying structural characteristics. The specification is silent on the representative examples for each class of compounds in terms of structural features, chemical formulae and structure-function relations. Therefore the claims as recited and the specification as disclosed is inadequate in providing support for the invention as recited.

The claim 3 recites that the inhibitor is lipid soluble. The specification does not provide adequate description as to nature or structural features that constitute a lipid soluble molecule. Specification lacks written description to support this claim. There are innumerable number of

molecules that are lipid soluble in literature. A peptide that comprises of only hydrophobic amino acids or a peptide modified with a lipophilic moiety is lipid soluble molecule. Any molecule attached to a polyalkyl hydrocarbon chain will also be lipid soluble molecule. The claim as recited and specification as disclosed neither provide a proper definition nor any structural characteristics associated with the inhibitor that is lipid soluble.

The claim 4 of instant application recites that the inhibitor is a peptidyl chloromethylketone having a peptide moiety that mimics at least one Convertase enzyme site. To begin with the Convertase enzyme family itself is classified according to their distribution in various tissues and are classified into several subgroups (page 2 of Dubios reference). Mere recitation of peptidyl chloromethylketone having a peptide moiety that mimics at least one Convertase enzyme site does not provide adequate written description support to the invention without providing proper structural feature and chemical formulae that represents structure for the peptide analogs and the associated Convertase enzyme that the peptide inhibits.

The claims also recite that the method of the instant invention encompass applying furin inhibitor not only to a site of a wound or fibrotic disorder but also to a site where a wound may form or fibrosis may occur. The claim as recited implies that the furin inhibitor is applied to a site other than a site that requires the treatment implying that the furin inhibitor is applied to unknown sites on normal individuals in order to prevent the formation of scar where a wound has not formed and fibrosis has not occurred.

Therefore, the claim(s) as recited contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1-4, 8 and 12-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for reducing scarring or reducing fibrosis by applying a furin inhibitor to a site of wound or fibrotic disorder, does not reasonably provide enablement for a method for reducing scarring in the healing of wounds and reducing fibrosis by applying a furin inhibitor to a site where a wound may form or fibrosis may occur. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

In the instant application, applicants claim a method for reducing scarring during the healing of wounds, reducing fibrosis in the treatment of fibrotic conditions, or for preventing or inhibiting scar formation or fibrosis, comprising applying a furin inhibitor to a site of a wound or fibrotic disorder or to a site where a wound may form or fibrosis may occur.

The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in *Wands* states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations"

Art Unit: 1654

(Wands, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the amount of direction or guidance presented; (6) the presence or absence of working examples; and (7) the quantity of experimentation necessary.

While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

*(1) The nature of the invention and (2) the breadth of the claims:*

The claims are drawn to a method for reducing scarring during the healing of wounds, reducing fibrosis in the treatment of fibrotic conditions, or for preventing or inhibiting scar formation or fibrosis, comprising applying a furin inhibitor to a site of a wound or fibrotic disorder or to a site where a wound may form or fibrosis may occur. The claims as recited encompasses any and all furin inhibitors that belongs to several different classes of inhibitors as disclosed in the specification on page 9. However, the claims and specification discloses the names and structural features of only two furin inhibitors Dec-RVKR-CMK and hexa-arginine. The claims as recited also encompass not only a method wherein the furin inhibitor is applied to reduce scarring during wound healing and fibrosis but also a method of reducing the scarring during wound healing and fibrosis by applying the furin inhibitor to sites where a wound may form and fibrosis may occur. Thus, the claims as recited imply that the invention as claimed is treating unknown sites on patients who may or may not suffer wounds and fibrosis at those sites. Thus the claims as recited is not enabled, and does not enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

*(3) The state of the prior art and (4) the predictability or unpredictability of the art:*

The state of the prior art as disclosed by Dubois teaches that furin and furin-like inhibitors are useful in treating wound healing and fibrosis. The reference discloses PDX or a construct, variant, analog, peptide, peptidomimetic, salt and derivatives thereof in the preparation of pharmaceutical compositions for the inhibition of furin or furin-like protease activity in inflammatory and erosive diseases that includes pulmonary fibrosis, abnormal wound healing and arthritis and others. Furin or furin-like protease activity includes the activity of proprotein convertases such as PACE4, PC5/6 or PC7/8.

Pearton, et al., discloses the elected species decanoyl-RVKR-cmk. The cited reference of Pearton teaches that the decanoyl-RVKR-cmk as a peptide PC inhibitor inhibits the cleavage of Notch-1, a receptor important in cell fate determination and is found throughout the epidermis (Abstract). The decanoyl-RVKR-cmk is a chloromethyl ketone peptide. The reference teaches that a protease family that has been implicated in processing and differentiation in a number of tissues is the Proprotein Convertase (PC) family.

The information available on the website:

'<http://www.nlm.nih.gov/medlineplus/ency/article/000484.htm>' indicates that treatment for the glomerulonephritis depend on the cause and severity of symptoms and the primary goal is to control the symptoms (page 3, under the subheading 'Treatment') and clearly states that there is no specific prevention for most causes of glomerulonephritis, although some cases may be



Art Unit: 1654

prevented by avoiding or limiting exposure to organic solvents, mercury and non-steroidal anti-inflammatory analgesics.

The information available on the website: '<http://www.pulmonaryfibrosis.org/ipf.htm>' clearly states that there are currently no effective treatments or a cure for pulmonary fibrosis (page 2, under the subtitle 'How it is treated?'). The cited reference further states that the pharmacological agents designed to treat lung scarring are still in experimental stage and treatments intended to suppress inflammation have only limited success in reducing the fibrotic progress.

The information available on the website: '<http://en.wikipedia.org/wiki/Cirrhosis>' on page 6 under the subtitle 'Treatment' clearly states that, 'traditionally, liver damage from cirrhosis can not be reversed, but treatment could stop or delay further progression and reduce complications'.

The nature of the prior art and the unpredictability associated with treatment and prevention of fibrotic disease conditions as discussed above clearly provides incite into difficulties associated with treating scarring during wound healing and fibrosis and prevention of the same. The references of Dubois, Pearton teaches the method of treating wound healing and fibrosis using furin and furin-like inhibitors. The unpredictability in the art stems from the fact that fibrotic disease conditions such as glomerulonephritis, pulmonary fibrosis and cirrhosis although treatable to control the symptoms, they cannot be prevented or cured as illustrated above. Therefore, the claim as recited with regards to applying furin inhibitors to sites at which wound may form and fibrosis may occur is not enabled due to unpredictability of the art as

Art Unit: 1654

discussed above. Since the treating the fibrotic disorders remains largely unsolved, means for preventing the same remain highly unpredictable.

*(5) The amount of direction or guidance presented and (6) the presence or absence of working examples:*

The specification provide details of two experiments wherein the applicants study the inhibition of furin activity that inhibits TGF- $\beta$  (transforming growth factor- $\beta$ ) activation by thrombin activated platelets and they also show that furin like enzymes are involved in platelet-mediated latent TGF-activation. The experiments illustrated in the specification are in vitro examples using human platelets. The claims are drawn to a method for reducing scarring during healing of wounds and reducing fibrosis in the treatment of fibrotic conditions applying any and all furin inhibitors to a site of a wound or fibrotic disorder and the method also encompasses applying furin inhibitors to a site where a wound may form or fibrosis may occur. The claims as recited encompasses any and all known and unknown furin inhibitors to treat and prevent scarring during wound healing and reduce fibrosis in fibrotic disorder. The amount of direction or guidance provided in the specification in the form of two examples (in vitro studies) is vastly inadequate to commensurate with the scope of the claims as recited. In light of the unpredictability of the art in treating the fibrotic disorder as afore-described in the previous section, the amount of guidance provided to practice the invention is inadequate given the scope of the claims that are very broad.

*(7) The quantity of experimentation necessary:*

Considering the state of the art as discussed by Dubois that furin and furin-like inhibitors are useful in treating wound healing and fibrosis. The reference discloses PDX or a construct, variant, analog, peptide, peptidomimetic, salt and derivatives thereof in the preparation of pharmaceutical compositions for the inhibition of furin or furin-like protease activity in inflammatory and erosive diseases that includes pulmonary fibrosis, abnormal wound healing and arthritis and others. Pearton, et al., discloses the elected species decanoyl-RVKR-cmk. The cited reference of Pearton teaches that the decanoyl-RVKR-cmk as a peptide PC inhibitor inhibits the cleavage of Notch-1, a receptor important in cell fate determination and is found throughout the epidermis (Abstract). The decanoyl-RVKR-cmk is a chloromethyl ketone peptide. The reference teaches that a protease family that has been implicated in processing and differentiation in a number of tissues is the Proprotein Convertase (PC) family.

The information available on the website:

'<http://www.nlm.nih.gov/medlineplus/ency/article/000484.htm>' indicates that treatment for the glomerulonephritis depend on the cause and severity of symptoms and the primary goal is to control the symptoms (page 3, under the subheading 'Treatment') and clearly states that there is no specific prevention for most causes of glomerulonephritis.

The information available on the website: '<http://www.pulmonaryfibrosis.org/ipf.htm>' clearly states that there are currently no effective treatments or a cure for pulmonary fibrosis (page 2, under the subtitle 'How it is treated?'). The cited reference further states that the pharmacological agents designed to treat lung scarring are still in experimental stage and treatments intended to suppress inflammation have only limited success in reducing the fibrotic progress.

The information available on the website: '<http://en.wikipedia.org/wiki/Cirrhosis>' on page 6 under the subtitle 'Treatment' clearly states that, 'traditionally, liver damage from cirrhosis can not be reversed, but treatment could stop or delay further progression and reduce complications'.

Applicant have reasonably disclosed a method for reducing fibrosis using the elected spices of furin inhibitor decanoly-RVKR-cmk and hexa-arginine. However, the claims also encompass using the claimed method to **applying to a site where a wound may form or fibrosis may occur**, which is clearly beyond the scope of the instantly disclosed/claimed invention. The claim as recited implies that the method be used in normal individuals who do not have any symptoms of the disorder or who are not prone to such disorders. It is an improbable proposition to predict where a wound would form and who would develop fibrosis.

The nature of the prior art and the unpredictability associated with treatment and prevention of fibrotic disease conditions as discussed above clearly provides incite into difficulties associated with treating scarring during wound healing and fibrosis and prevention of the same. The references of Dubois, Pearton teaches the method of treating wound healing and fibrosis using furin and furin-like inhibitors. The unpredictability in the art stems from the fact that fibrotic disease conditions such as glomerulonephritis, pulmonary fibrosis and cirrhosis although treatable to control the symptoms, they can be prevented or cured as illustrated above. Therefore, the claim as recited encompasses use of any and all furin inhibitors to treat not only reducing the scarring during wound healing and reducing fibrosis in the treatment of fibrotic conditions, it encompasses applying furin inhibitors to a site where a wound may form and fibrosis may occur. The specification is clearly not enabled for the latter. The fact that the

Art Unit: 1654

method of the instant invention recites any and all furin inhibitors (several different classes of compounds listed on page 9 of the specification), the amount of guidance provided in the specification in the form of two working examples are clearly inadequate. One of ordinary skill in the art would be burdened with testing any and all furin inhibitors for the desired function of reducing scarring during wound healing and reducing fibrosis in the treatment of fibrotic conditions.

It is the Examiner's position that one skilled in the art would not be able to practice the invention commensurate with the scope of the claims without undue experimentation. It is also noted, considering the *a priori* unpredictability in the art with regard to treating fibrotic disorder associated with pulmonary fibrosis, glomerulonephritis and cirrhosis as discussed above, the treatment and prevention of the same is not enabled commensurate with the scope of the invention. Therefore, the claim(s) as recited contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

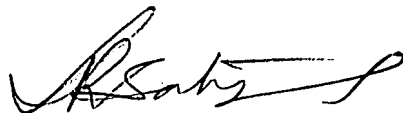
### ***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Satyanarayana R. Gudibande whose telephone number is 571-272-8146. The examiner can normally be reached on M-F 8-4.30.

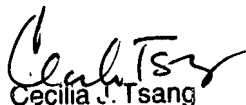
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Art Unit: 1654

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